Kidney International, Vol. 56, Suppl. 71 (1999), pp. S-242–S-244

Lipoprotein(a) as a risk factor for coronary artery disease in hemodialysis patients

Hiroshige Ohashi, Hiroshi Oda, Michiya Ohno, Sachiro Watanabe, and Shigeki Sakata

Division of Nephrology and Division of Cardiology, Prefectural Gifu Hospital, and Joto Clinic of Internal Medicine, Gifu, Japan

Lipoprotein(a) as a risk factor for coronary artery disease in hemodialysis patients.

Background. We studied whether lipoprotein(a) [Lp(a)] is an independent risk factor for coronary artery disease (CAD) in hemodialysis (HD) patients.

Methods. A serum concentration of Lp(a) was measured in 212 patients with chronic glomerulonephritis and 56 patients with diabetic nephropathy (a total of 268 patients). The causes of death during five years of follow-up were studied and classified into either cardiovascular or noncardiovascular events.

Results. The mortality of these 268 HD patients during the observation period was 26.1%. Seventy-eight percent were due to cardiovascular events. Those who died of cardiovascular events had significantly higher serum Lp(a) levels than those died of noncardiovascular events. The relative risk of death from CAD was 0.71 in HD patients with a Lp(a) concentration above 30 mg/dl.

Conclusions. This study indicates that the serum Lp(a) levels are independent indicators of the future risk of death from CAD in HD patients.

Lipoprotein(a) [Lp(a)] is a cholesterol-rich lipoprotein with structural similarities to low-density lipoprotein (LDL) and contains apolipoprotein (a) [apo (a)], which is a glycoprotein with sequence homology to plasminogen [1]. Lp(a) was considered as an independent risk factor for cardiovascular events in the general population [2]. Although an elevated concentration of Lp(a) levels in hemodialysis (HD) patients has been reported [3], it is still not clear whether Lp(a) plays a key role in the occurrence of cardiovascular events in HD patients. This study was done so as to clarify the role of serum Lp(a) on the fatal cardiovascular events, especially coronary artery disease (CAD) in patients with HD treatment.

METHODS

From 1992 to 1997, we investigated the prognosis in 268 HD patients (153 male and 115 female, mean age 57.6, range 26 to 73 years). When the study was started, they had been already undergoing HD for an average of 68.6 months (range of 2 to 268 months). In every patient, HD was performed three times per week. The underlying diseases of 212 (79.1%) and 56 (20.9%) patients were chronic glomerulonephritis (CGN) and diabetic nephropathy (DN), respectively. All patients with DN had non–insulin-dependent diabetes mellitus (NIDDM). Clinical history, physical examination, and routine laboratory tests were performed at entry. A previous history of myocardial infarction or cerebrovascular accident as well as angina pectoris was considered as having pre-existing clinical events. All blood samples were obtained after an overnight fast before heparinization or initiation of HD. Serum Lp(a) concentrations were measured by enzyme-linked immunosorbent assay.

The causes of death during the five-year follow-up period were classified into either cardiovascular or noncardiovascular events. Cardiovascular events were cerebrovascular disease (CVD), CAD, and aneurysmal rupture. Noncardiovascular events included malignancies and infectious and other miscellaneous diseases.

Values were expressed by means ± SD. Difference was evaluated by a nonpaired *t*-test and a chi-squared test. Cox regression analyses were used to detect the independent variables that could influence the death from CAD.

RESULTS

Follow-up and clinical events

Among 268 HD patients, 70 patients (26.1%) died during the five-year observation period (Table 1). Forty nine of them (70.0%) were by cardiovascular and the remaining 21 (30.0%) were by noncardiovascular events. Among 49 patients who died of cardiovascular events, 26, 22, and 1 were CVD, CAD, and aneurysmal rupture of thoracic aorta, respectively. Of 22 patients who died of CAD, congestive heart failure caused by old myocardial infarction and myocardial infarction accounted for 7 and 15, respectively.

Key words: cardiovascular disease, diabetic nephropathy, glomerulonephritis.

Table 1. Causes of death in hemodialysis patients

Clinical event	*N*
Cardiovascular event	
Cerebrovascular disease	26
Cerebral hemorrhage	(15)
Cerebral infarction	(7)
Subarachinoid hemorrhage	(4)
Coronary artery disease	22
Congestive heart failure due to old myocardial infarction	(7)
Myocardial infarction	(15)
Aneurysmal rupture	1
Noncardiovascular event	
Malignant disease	9
Gastric cancer	(2)
Colon cancer	(5)
Lung cancer	(1)
Prostate cancer	(1)
Infectious disease	8
Pneumonia	(4)
Sepsis	(3)
Peritonitis	(1)
Miscellaneous disease	4
Cachexia	(4)

Table 2. Multiple logistic regression analysis of risk factors for death due to coronary artery disease in HD patients

Variable	Relative risk
Gender *male*	0.47
Age *years*	−0.02
Duration of HD *months*	−0.01
Smoking	0.23
TC *220 mg/dl* <	−0.44
HDL-C *40 mg/dl* >	−0.17
Lp(a) *30 mg/dl* <	0.71[a]
Diabetic nephropathy	0.50

Abbreviations are: HD, hemodialysis; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; Lp(a), lipoprotein(a).

[a] $P < 0.05$

Characteristics of hemodialysis patients who died of cardiovascular events

Compared with HD patients who died of noncardiovascular events, those who died of cardiovascular events had characteristics of a large number of DN patients, a long-term HD period, and higher Lp(a) levels [Lp(a) was 29.3 ± 22.0 mg/dl in patients with cardiovascular events ($N = 49$) vs. 19.5 ± 13.8 mg/dl in patients without cardiovascular events, ($N = 21$), $P < 0.05$].

Characteristics of hemodialysis patients who died of coronary artery disease

Compared with HD patients who died of CVD, those who died of CAD had characteristics of old age, male gender, and higher Lp(a) levels [Lp(a) was 34.4 ± 19.0 mg/dl in CAD ($N = 22$) vs. 22.4 ± 18.6 mg/dl in CVD ($N = 26$), $P < 0.05$].

Analysis of risk factors for death from coronary artery disease in hemodialysis patients

Male gender, age, duration of HD, smoking, high total cholesterol, low high-density lipoprotein cholesterol levels, and DN were independent contributors to the increased risk of CAD mortality (Table 2). Baseline Lp(a) levels higher than 30 mg/dl were the sole independent risk factors by multiple logistic regression analysis (relative risk, 0.71).

DISCUSSION

Lipoprotein(a) levels above 30 mg/dl are considered to be high according to our previous report [4]. The number of 268 HD patients with high Lp(a) levels was 96 (35.8%). This is significantly higher than that seen in normal subjects (12.3%) [4]. During the five-year observation period, 70 HD patients (26.1%) died. Among the 70 deaths, 49 of them died of cardiovascular events. Among 49 HD patients who died of cardiovascular events, 26 and 22 were CVD and CAD, respectively. The clinical characteristics of HD patients who died of CAD were patients with DN, less female gender and high Lp(a) levels compared with those who died of CVD. From the multiple logistic regression analysis of risk factors for death caused by CAD, it is suggested that the Lp(a) level is an independent risk factor for CAD. Considering these results, the use of effective pharmacological agents such as nicotinic acid and/or LDL apheresis to reduce Lp(a) levels in HD patients will provide the opportunity to test the hypothesis that Lp(a) is a modifiable risk factor for the death of CAD in HD patients.

Lipoprotein(a) is a lipoprotein that has apo B-100 and apo (a) as an apolipoprotein that has high homology with plasminogen [1]. It has recently been proposed that Lp(a) is atherogenic lipoprotein. The proposed mechanisms are as follows. First, Lp(a) interfered with several steps in the clotting and fibrinolysis cascade [5]. Second, the cholesterol content of Lp(a) is low compared with LDL, but oxidized Lp(a) deposit easily and stay in the arterial walls for a longer period [6]. Third, Lp(a) promotes proliferation of smooth muscle cells by inhibiting plasminogen, which, in turn, reduces the activation of transforming growth factor-β, an inhibitor of cell proliferation [7]. With such reports, together with this study, it is reasonable to conclude that high Lp(a) levels may contribute to coronary artery sclerosis in HD patients.

In summary, we suggest that HD patients with higher Lp(a) levels have more of a chance of death from cardiovascular events, especially CAD, and therefore, careful observations are needed in these patients. We should strictly manage not only Lp(a) levels, but also other risk factors in all HD patients with higher Lp(a) levels.

Reprint requests to Hiroshige Ohashi, M.D., Division of Nephrology, Prefectural Gifu Hospital, 4-6-1 Noishiki, Gifu 500-8717, Japan.

REFERENCES

1. Uterman G: The mysteries of lipoprotein(a). *Science* 246:904–916, 1989
2. Rosengren A, Wilhelmsen L, Eriksson E, Risberg B, Wedel H: Lipoprotein(a) and coronary heart disease: A prospective case-control study in a general population sample of middle-aged men. *BMJ* 301:1248–1251, 1990
3. Cressman MD, Heyka RJ, Paganini EP, O'Neil J, Skibinski CI, Hoff HF: Lipoprotein(a) is an independent risk factor for cardiovascular disease in hemodialysis patients. *Circulation* 96:475–482, 1992
4. Ohashi H, Oda H, Matsuno Y, Watanabe S, Kotoo Y, Abe A, Noma A, Sawada S, Hirano T, Ishiguro M: Lp(a) lipoprotein in patients on maintenance hemodialysis: A study from apo (a) isoform. *Jpn J Nephrol* 35:823–828, 1993
5. Howard GC, Pizzo SV: Lipoprotein(a) and its role in atherothrombotic disease. *Lab Invest* 69:373–386, 1993
6. Sandkamp M, Funke H, Schulte H, Kohler E, Assmann G: Lipoprotein(a) is an independent risk factor for myocardial infarction at a young age. *Clin Chem* 36:20–23, 1990
7. Grainger DJ, Kirschenlohr HL, Metcalfe JC, Weissberg PL, Wade DP, Lawn RM: Proliferation of human smooth muscle cells promoted by lipoprotein(a). *Science* 260:1655–1656, 1993